The Role of Early Clinic Research/Clinical Pharmacology Trial Centers in Precision Medicine Research

Symposium 7:
Global Initiatives: Collaboration and Best Practices Forum

Presented by:
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Vice President, Strategic Development, Celerion
“Decision Gates” in Drug Development

Questions that need an answer
- Design and conduct studies
- Analyze results relative to key questions

New questions for next gate
- Design and Cost Studies
- Availability of further investment?

Go / No Go Decision
- Yes: Proceed to next decision gate
- No: STOP

Three Important Factors
- Decision Process → who decides?
- Timing relative to resources, competition
- Quality of Information → role of biomarkers
# Go / No Go Decision Gates in Drug Development

<table>
<thead>
<tr>
<th>Decision Gate</th>
<th>Question</th>
<th>Decision-Maker(s)</th>
<th>Role of Biomarkers</th>
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</thead>
<tbody>
<tr>
<td>Disease Target</td>
<td>Does a drugable target exist that impacts disease progression?</td>
<td>Scientist</td>
<td>Defining mechanism of action</td>
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<tr>
<td>Lead Candidate</td>
<td>Does a suitable drug candidate exist with properties predicted to impact disease in a positive way?</td>
<td>Scientist, Sponsor</td>
<td>Impact on disease, Drug delivery to site of action</td>
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<tr>
<td>First-in-Human</td>
<td>Can the drug candidate be given safely to humans?</td>
<td>Sponsor, Regulators, IRB/EC Investigators</td>
<td>Impact on disease, Safety measures of clinical relevance</td>
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<tr>
<td>Clinical Proof-of-Concept</td>
<td>Does the drug work in humans as it was designed?</td>
<td>Sponsor</td>
<td>Confirming mechanism of action in humans, Impact on disease, Defining dose-limiting toxicity</td>
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<td>Begin Phase 3</td>
<td>Can dosage, target patient populations, and pivotal efficacy and safety study designs be justified?</td>
<td>Sponsor, Regulators</td>
<td>Impact on disease / dose-response, Patient selection, Patient safety</td>
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<tr>
<td>Marketing Application</td>
<td>Has safe and effective use of the drug been proven?</td>
<td>Regulators</td>
<td>Validated markers that may contribute to the confirmation of safety and efficacy</td>
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<td>Postmarketing Safety</td>
<td>Are there emerging safety issues that need further action?</td>
<td>Sponsors, Regulators</td>
<td>Predict patients more likely to experience rare events</td>
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</table>
Biomarkers Provide Data That Enable Better Decisions Early in Drug Development

• **Efficacy** Biomarkers – help establish “proof of mechanism” or “clinical proof-of-concept”
  – Specific for therapeutic target

• **Safety** Biomarkers – provide sentinels of toxicity
  – Apply broadly across therapeutic areas
  – Most useful if can catch serious toxicity early

• **Patient Selection** – allow investigators to choose likely responders over likely non-responders
  – Enriched responder cohorts reduce clinical study size
  – Form the basis for companion diagnostic tests
Important “Proofs” in Early Clinical Research

Key Role of Biomarkers

- **Proof-of-Presence (Phase 1)**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism (Phase 1 or 2)**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept (Phase 2)**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

- **Pharmacokinetics**
- **Tissue concentrations**
- **Healthy subjects (HS) or patients**

- **Biomarkers reflecting target engagement**
- **Biomarkers of toxicity (liver, kidney effects)**
- **Healthy subjects or patients**

- **Biomarkers reflecting impact on disease**
- **Biomarkers of toxicity (liver, kidney effects)**
- **Patients**
## Highly Targeted Drugs – Easier or Harder?

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<tr>
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<th>Easier</th>
<th>Harder</th>
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<tr>
<td><strong>Specificity of Effect</strong></td>
<td>Fewer off-target effects ➔ fewer AEs</td>
<td>Possible high potency and steep dose-response curve ➔ more difficult dose escalation</td>
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<td><strong>Biomarkers</strong></td>
<td>Can be specific ➔ provide valuable data for CPoC study</td>
<td>Often need to develop unique assays</td>
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<td><strong>Recruitment</strong></td>
<td>If standard of care is poor, attractive to patients and investigators</td>
<td>Difficult to find the right patient if other options exist</td>
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<td><strong>Conduct</strong></td>
<td>Promising targeted drugs will attract quality investigators</td>
<td>Complex sample and patient logistics</td>
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<td><strong>Regulatory</strong></td>
<td>Orphan classification can provide faster time to approval</td>
<td>May require companion diagnostic tests</td>
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Strategic Approach: Build a Bridge Backwards

Start design of CPoC study first

• What is “Proof”? Endpoints?
• What patients? How many?

How to get to CPoC?

• What can I do in healthy subjects?
• Are biomarkers available?
• Develop novel biomarkers?
  – Biochemical assays
  – Imaging and imaging agents
  – MicroRNA panels
• Would microtracer studies be valuable?
• Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?
Early Signals of Clinical Safety and Efficacy are the Key to Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

- Patients
  - Small number
  - Stable disease
  - Minimal confounding treatments
  - Appropriately motivated

- Investigators / Clinical Trial Units
  - Small number of sites
  - Scientifically / medically robust
  - Controlled study setting
  - Follow global GCP standards
  - Ethical
Clinical Trial Units Must Have:

- Facilities for confined studies in a highly controlled environment
- Well trained staff competent in GCP regulations
- Access to patients suitable for early clinical research studies
- Ability to manage the logistics of complex, time-dependent procedures
# Celerion Audit Results of 7 Asian CTCs
## 2013-2014

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<th>Category</th>
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- Inadequate or missing
- Work needed to pass global audit
- Some changes needed to pass global audit
- Acceptable for global audit
Challenge: Recruiting Patients to Early Clinical Research Studies

- Not a single disease
- Non-therapeutic doses
- Treatment withdrawal
- Disease prevalence
- Study criteria
- Specialist involvement
- Co-medication
- Willingness patient
- Alternative treatment
Challenge: Complex sample collection schedules and processing procedures

Example: First-in-Patient study – 14 tests, 7 labs

Lab D
Pharmacogenomic assay

Lab B
Clinical chemistry

Lab G
Future proteomics

Lab C — LC/MS/MS assay pathophysiological substrate and product

Lab E
Target enzyme assays

Lab F
Stimulated cell assay

Lab A
LC-MS/MS assay parent drug and metabolites

Lab B
Urinalysis

Add stabilizer

Non-coagulated blood

Add stabilizer

Freeze

Freeze

Heparinized blood

Plasma

Serum

WBCs

Tissue Biopsy

Urine
Specialty Clinical Trial Units
Celerion’s Respiratory Center of Excellence
Belfast, UK

- Spirometry
- Bronchoalveolar Lavage
- Challenge Models
- Body Plethysmography
- Fractional Exhaled Nitric Oxide Testing
- Lung Clearance Index
Take Aways

• Precision medicine means more targeted drugs ➔ less off-target effects ➔ safer

• Early clinical research challenges include:
  – finding the right subject or patient
  – right biomarkers to demonstrate target selectivity
  – managing controlled clinical studies with complex sample logistics

• Specialized clinical trial units offer a good solution for early studies with precision medicines.
Thank You
Daedanhi Kamsahamnida